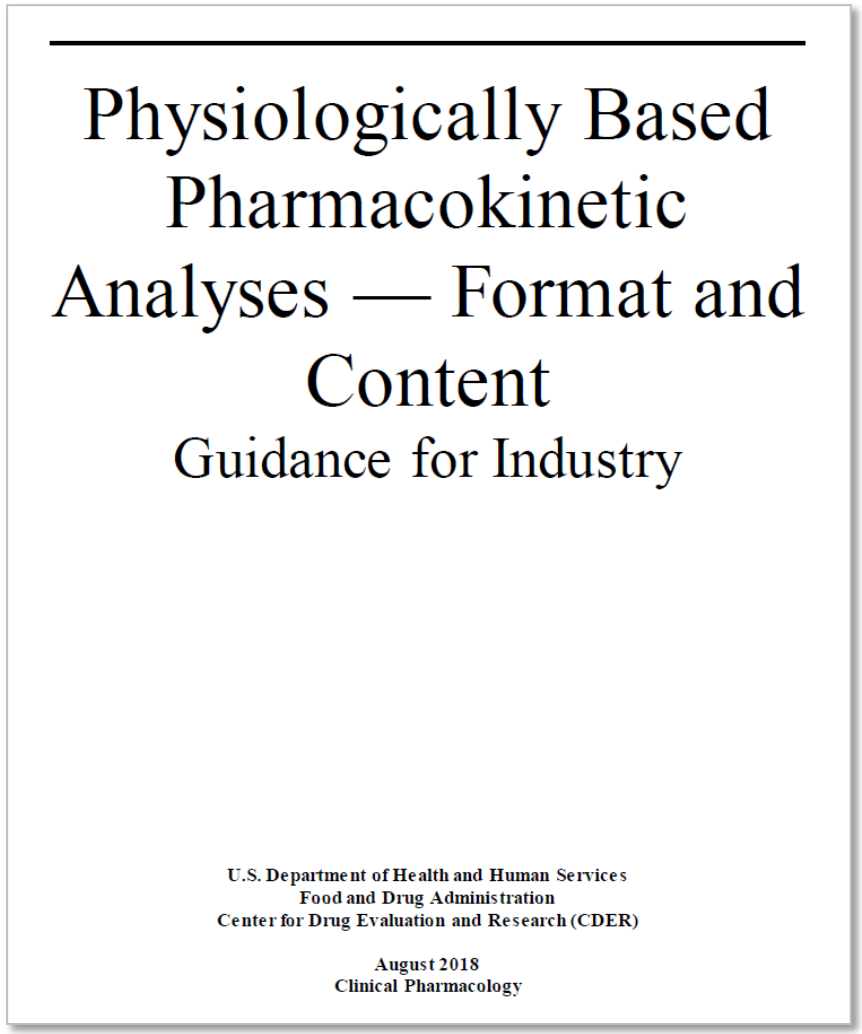
Best practices for model building:

Parameter optimization, sensitivity analysis and how to assess the match to clinical data

09/24/2019 / André Dallmann, Sebastian Frechen, Rolf Burghaus

Introduction

Guidance documents for PBPK analyses



Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Clinical Pharmacology

> This guidance does not address methodological considerations and best practices for the conduct of PBPK modeling and simulation […].

PBPK modeling approaches

Bottom-up • middle-out • top-down

Bottom-up approach:

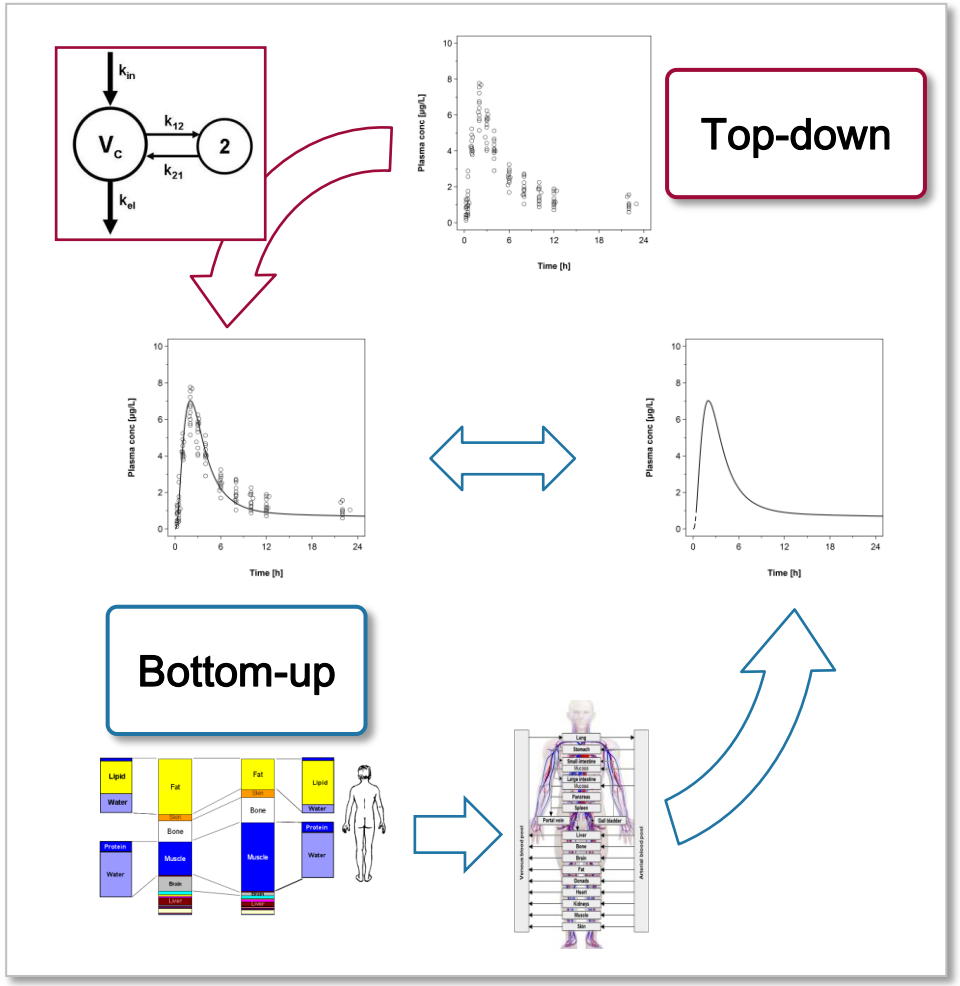
- Mechanism-driven model
- IVIVE
- Clinical PK data not used for model development

Top-down approach:

- Empirical model, data-driven
- Model structure/parameterization informed by clinical PK data

Middle-out approach:

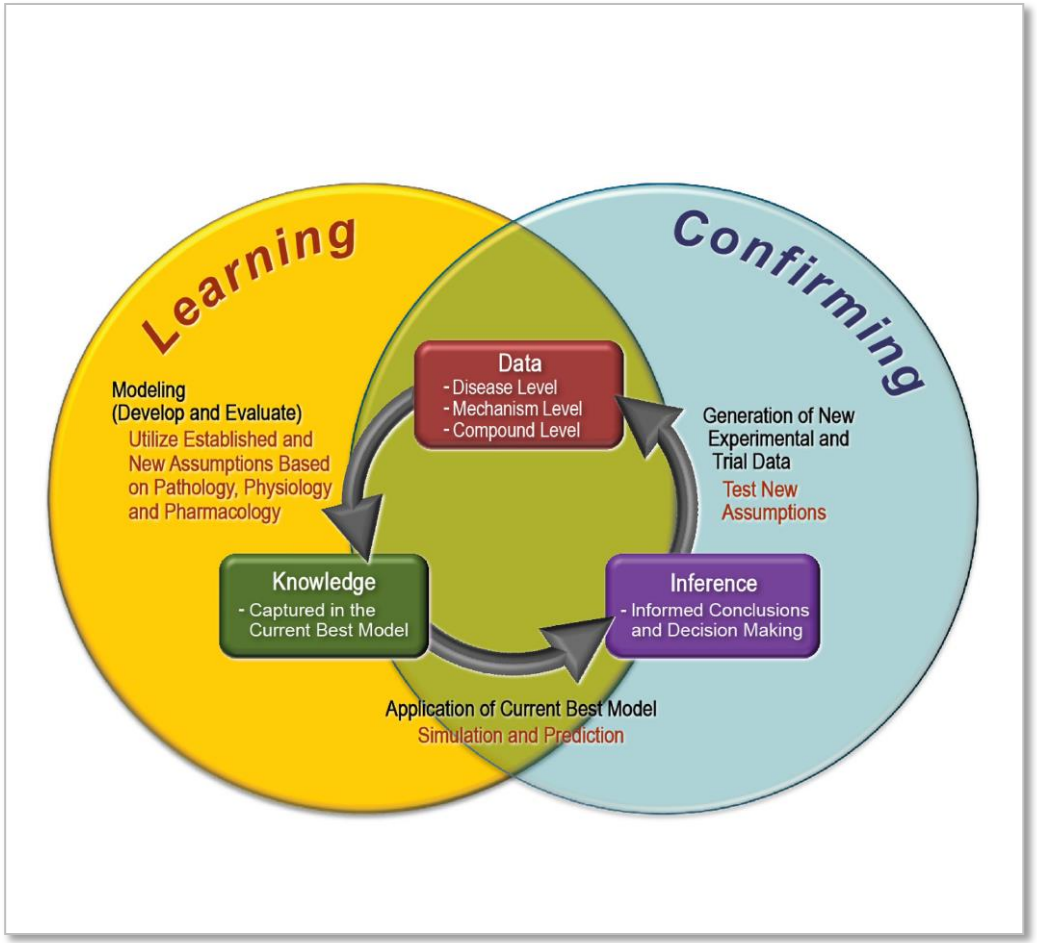
- Combination of the other two approaches
- Reverse translation & forward projection



The value of PBPK modeling

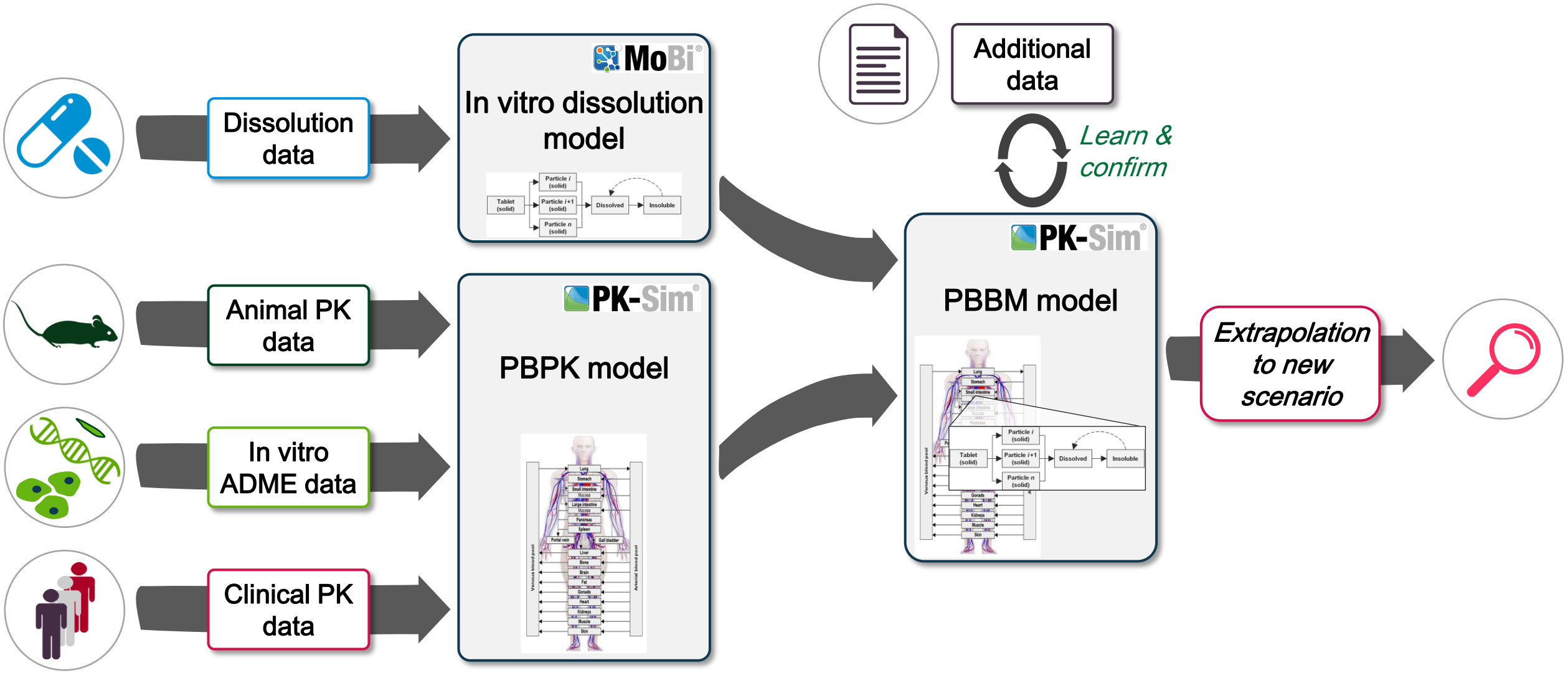
PBPK models facilitate mechanistic understanding and extrapolation to new scenarios

- “PBPK-thinking” involves a mechanistic understanding of pharmacokinetic processes
- If the confidence in a model to simulate observations in a specific system is sufficiently high, it can be used for:
  - Identification of parameters critical for a specific PK behavior
  - Establishing an in vitro–in vivo link between in vitro dissolution and in vivo absorption
  - Translation to a new scenario (“set of conditions”), e.g. prediction of in vivo exposure of different oral dosage forms

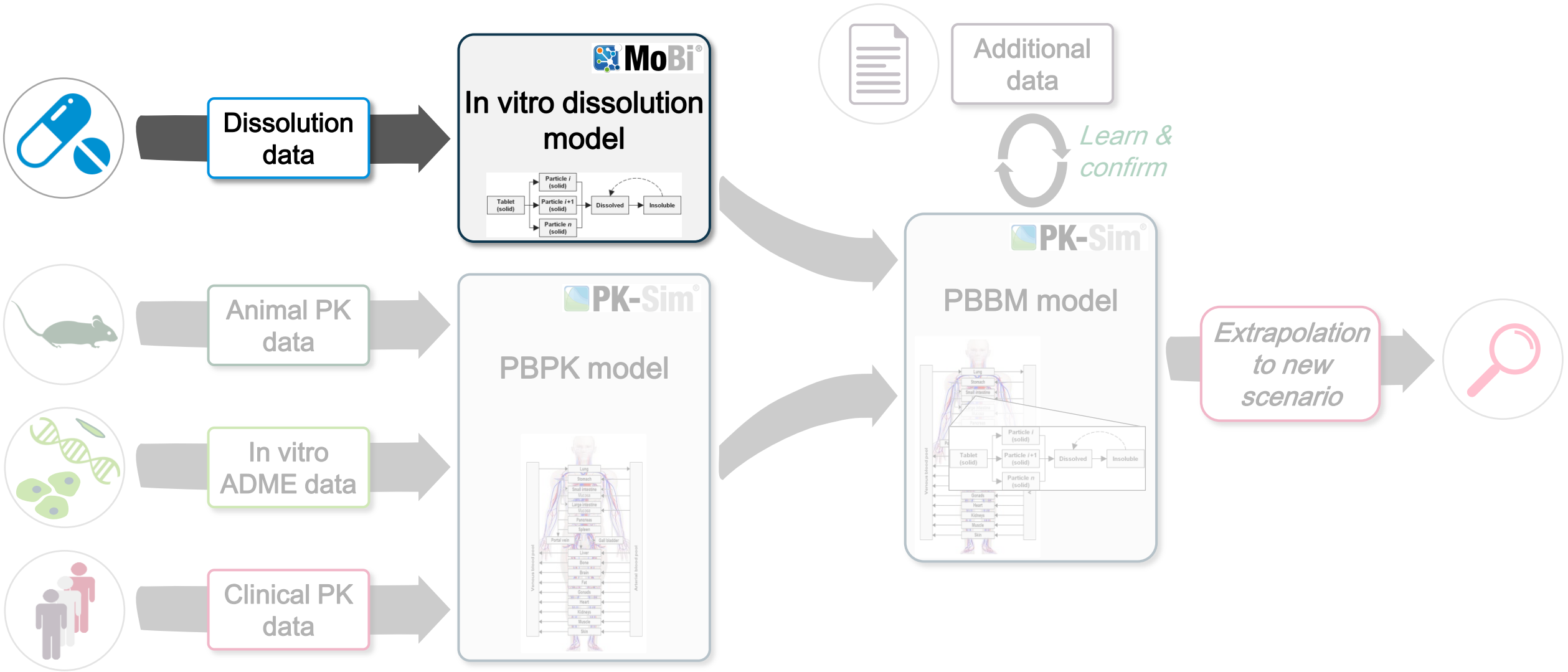


Marshall et al. 2016. doi: 10.1002/psp4.12049

Workflow for PBBM model development



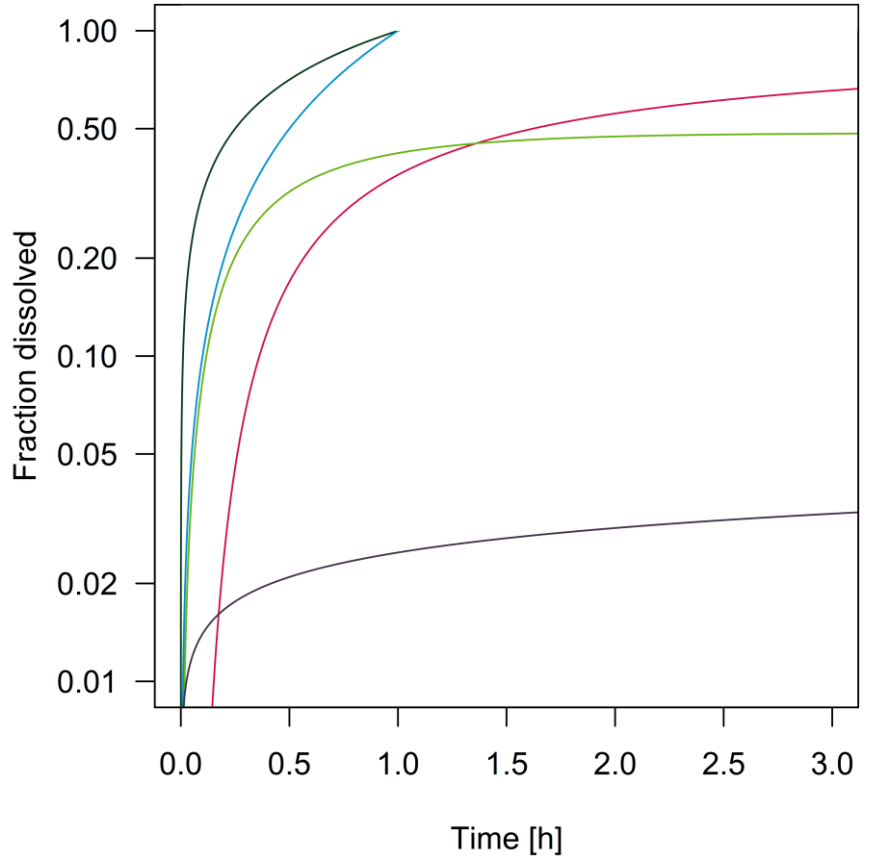
Workflow for PBBM model development



Establishment of a dissolution model

Multiple models can be used to describe a dissolution profile

Model	Description
Zero order model	e.g. for matrix tablets with poorly soluble drugs, coated forms, osmotic systems
Weibull model	empirical model useful for various types of formulations
Higuchi model	e.g. for matrix tablets with water soluble drugs
Johnson model	adapted Noyes-Whitney function useful for e.g. poorly soluble drugs with polydisperse particle size distributions
…	…



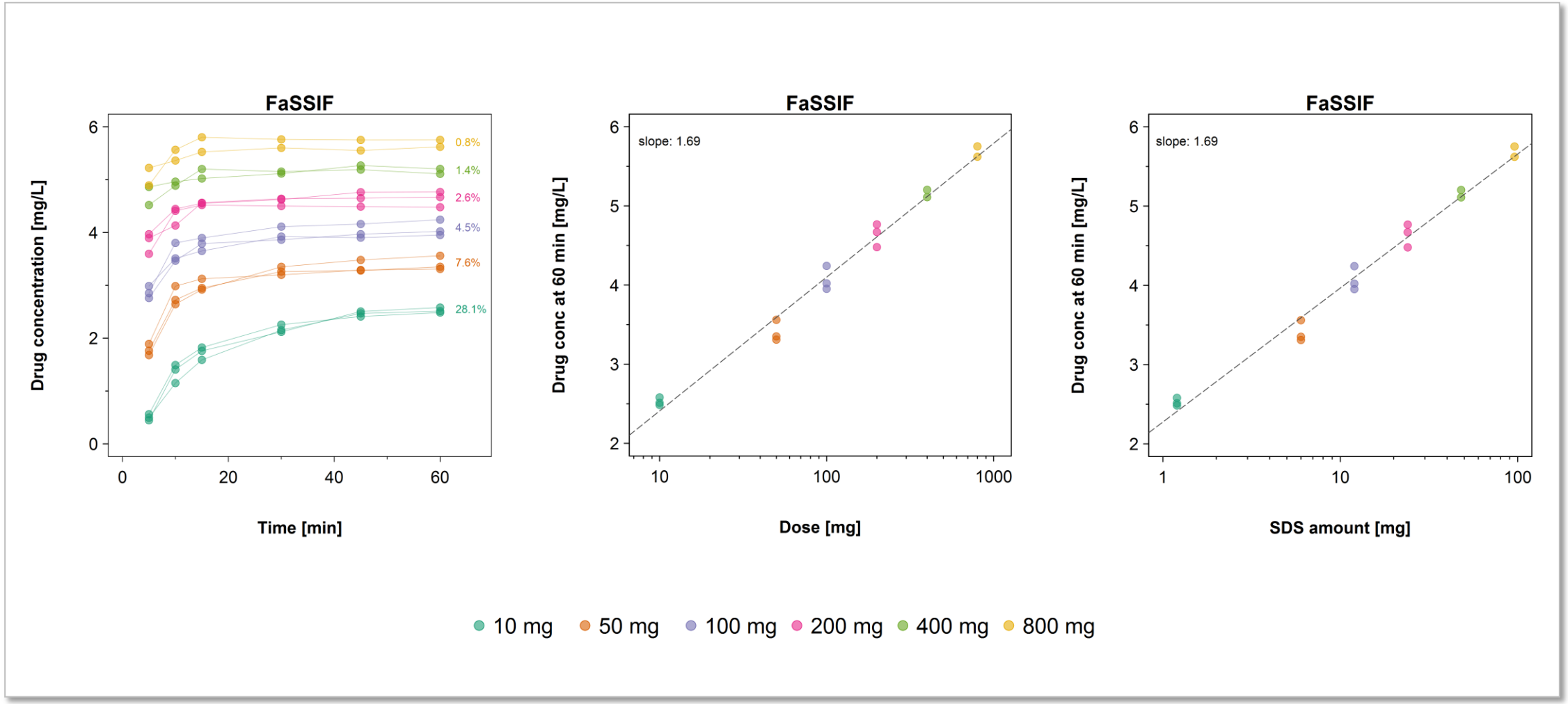
Establishment of a dissolution model

Recommendations for structural model selection

- Understand the science:
  - E.g. is there evidence for precipitation?
  - Are there factors affecting dissolution that are unaccounted for, such as surfactants?
- Explore different structural models
- Preferably use a mechanistic model → facilitate translation to the in vivo situation
  - Avoid empirical functions to describe dissolution kinetics (e.g. Weibull)

Establishment of a dissolution model

Example of dissolution data and inferred model



Establishment of a dissolution model

Example of dissolution data and inferred model

Structural model:

- Johnson model (Noyes-Whitney) for polydisperse particles
- Log-linear relationship between SDS concentration in medium and the drug‘s saturation concentration was integrated in the Johnson model

Parameter optimization:

- All data were used (dissolution in all biorelevant media) → poorly fitted data can trigger revision of mechanistic understanding and underlying model structure

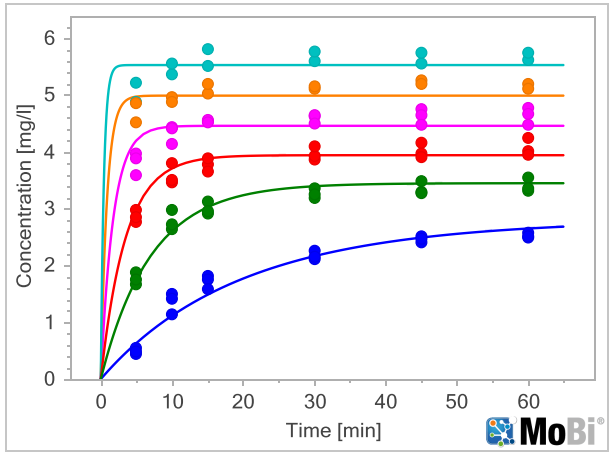
Optimized parameters:

- Aqueous diffusion coefficient
- Thermodynamic solubility in each medium (intercept)
- SDS-effect on solubility (slope)

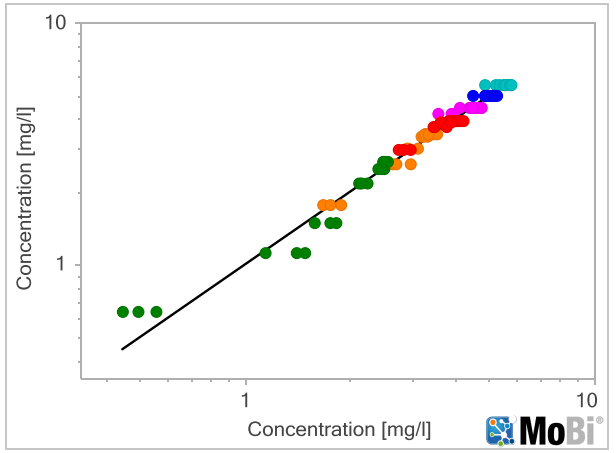
Establishment of a dissolution model

Visual assessment of the consistency between data and structural model/error model

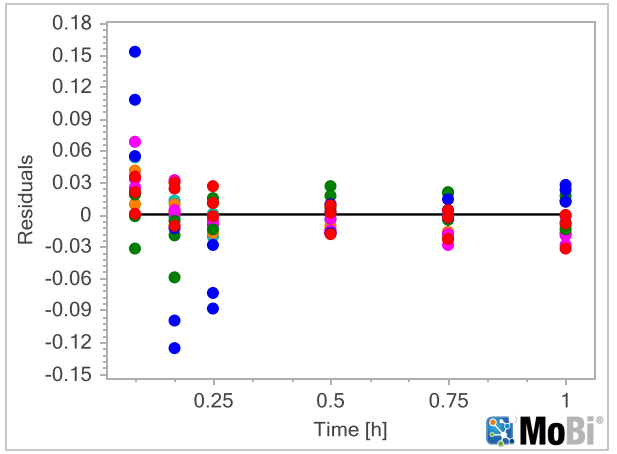
Concentration-time profiles



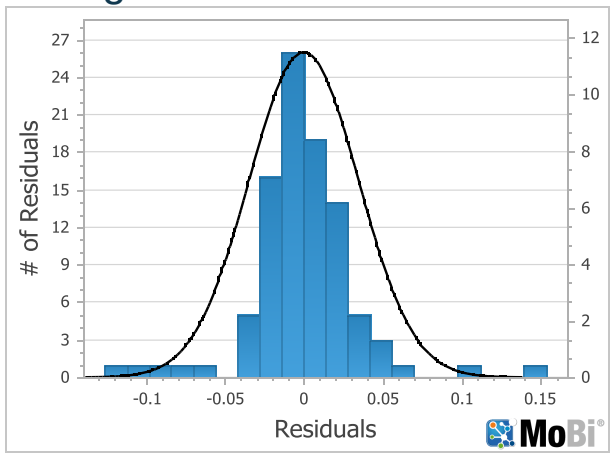
Simulated vs. observed



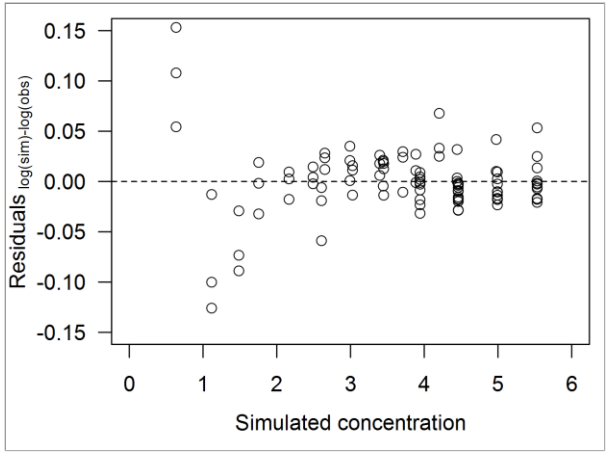
Residuals vs. time



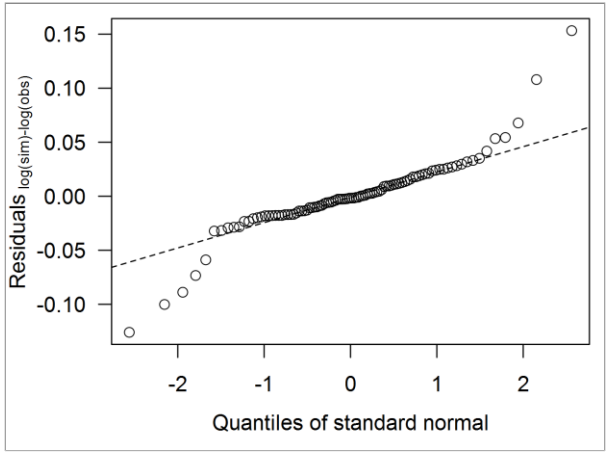
Histogram of residuals



Residuals vs. simulated

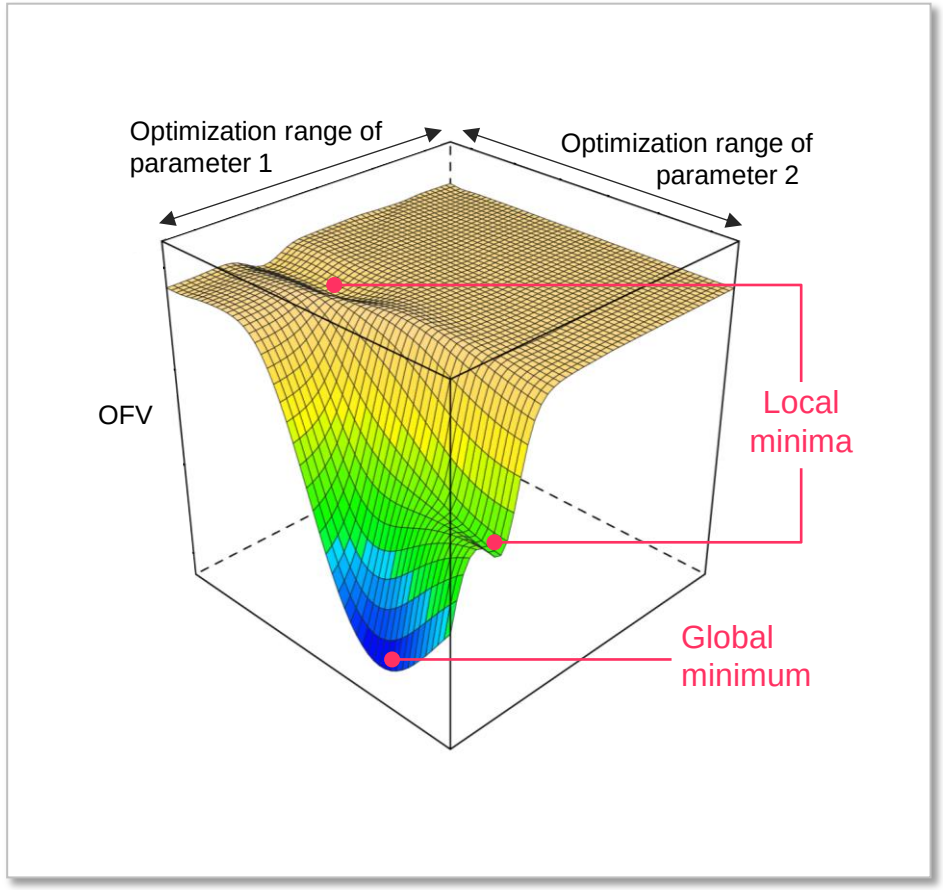


Quantiles vs. quantiles



Establishment of a dissolution model

Non-identifiable parameters and high uncertainty pose a risk to model translation



95% Confidence interval

Identification Parameter	95% Confidence Interval
Aqueous diffusion coefficient	4.33E-6 +- 3.99E-7 [dm²/min]
Solubility	1.85 +- 0.24 [mg/l]
SDS-effect on solubility	0.79 +- 0.08

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Correlation between uncertainties in parameter estimates

-1.00 -0.50 0 0.50 1.00

	Aqueous diffusion coefficient	Solubility	SDS-effect on solubility
Aqueous diffusion coefficient	1.00	-0.77	0.63
Solubility	-0.77	1.00	-0.94
SDS-effect on solubility	0.63	-0.94	1.00

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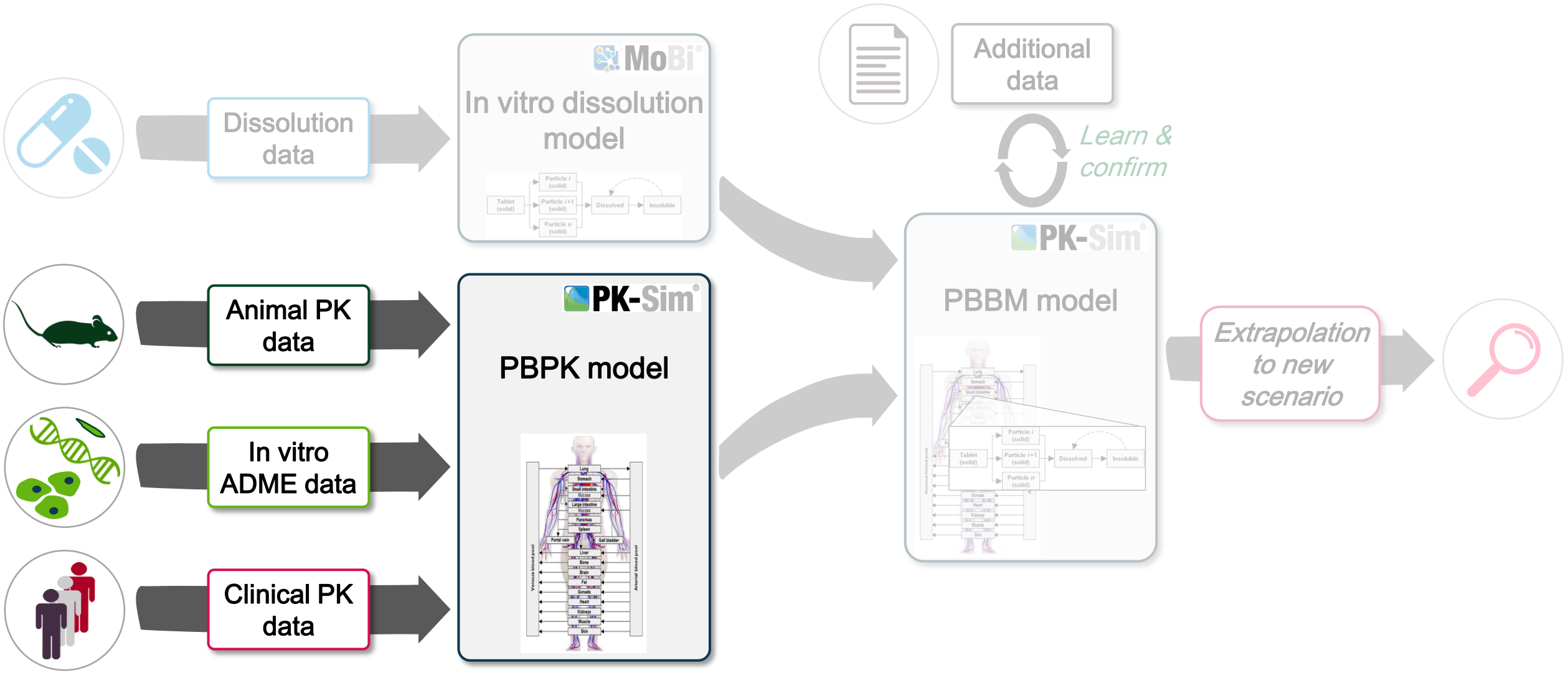
Establishment of a dissolution model

Recommendations for parameter optimization of dissolution models

- Visually inspect consistency between data and model, e.g. through:
  - Concentration-time profiles
  - Goodness-of-fit plots
  - Residuals vs. time
  - Residuals vs. simulation
  - Histogram of residuals
  - Quantiles vs. quantiles
- Evaluate non-identifiability issues, imprecise parameter estimates and strong correlations between optimized parameters
- Take measures to avoid local minima, e.g.:
  - If the optimized parameter value is close to the upper or lower bound, modify the bound and repeat the optimization
  - Randomize start values of optimized parameters
  - Instead of a greedy algorithm, use a more robust optimization algorithm (e.g. MCMC, simulated-annealing)

Workflow for PBBM model development



Establishment of a PBPK model

Example of PBPK model optimization

Structural model:

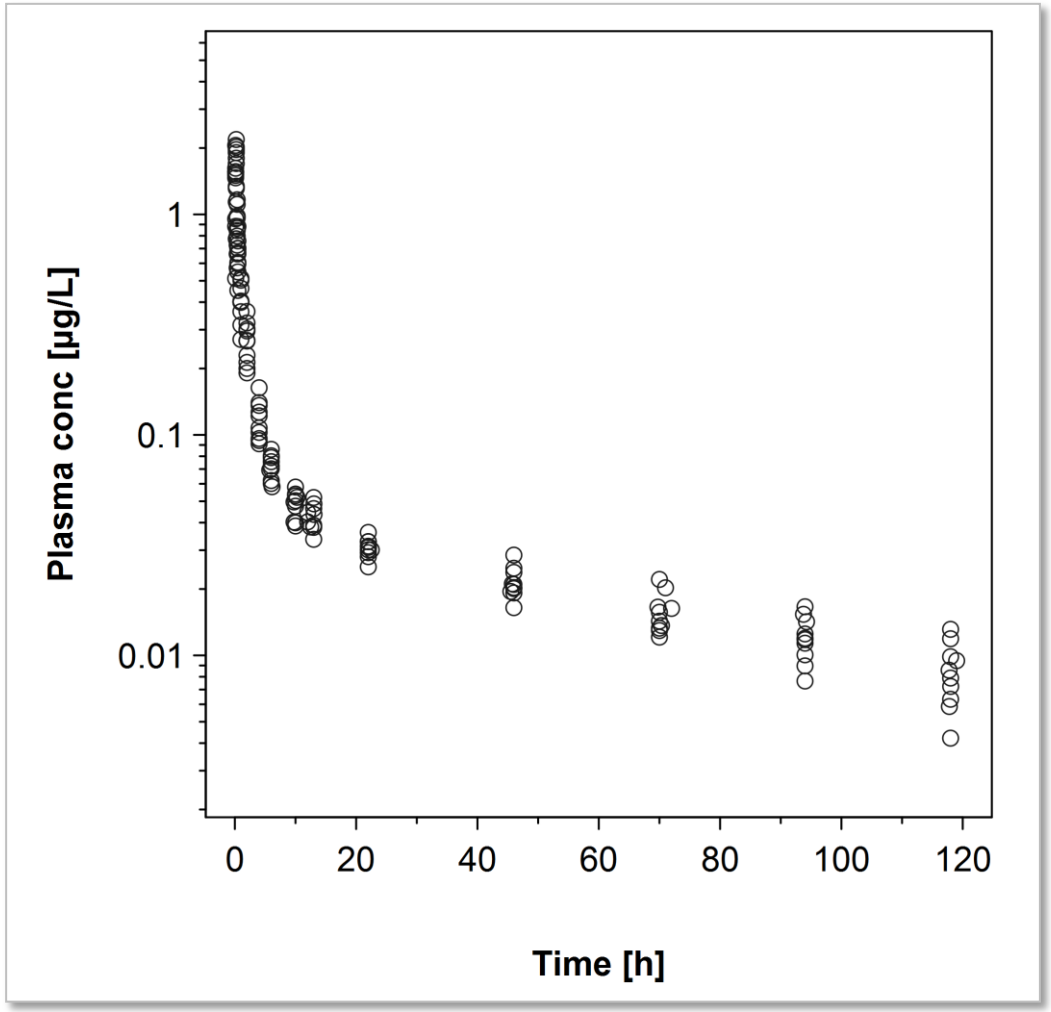
- Whole-body PBPK model for a CYP3A-metabolized drug with minimal renal excretion

Parameter optimization:

- Testing of different models for partition coefficients

Optimized parameters:

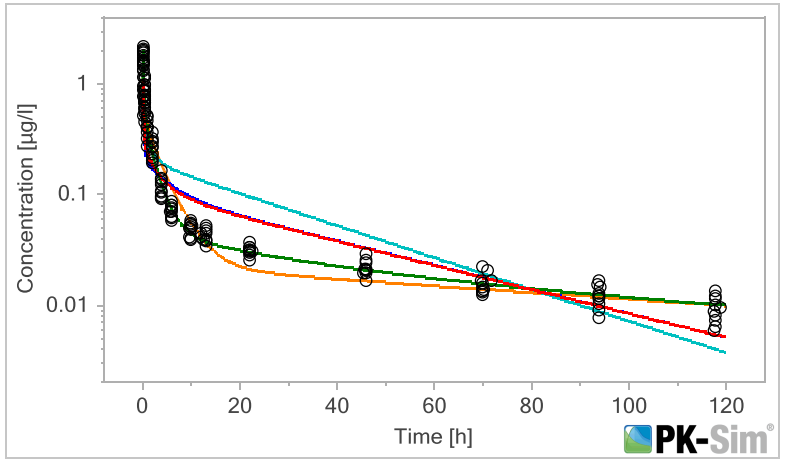
- CYP3A CL, GFR fraction and lipophilicity fitted to IV data
  → thereafter fixed in oral PBPK model



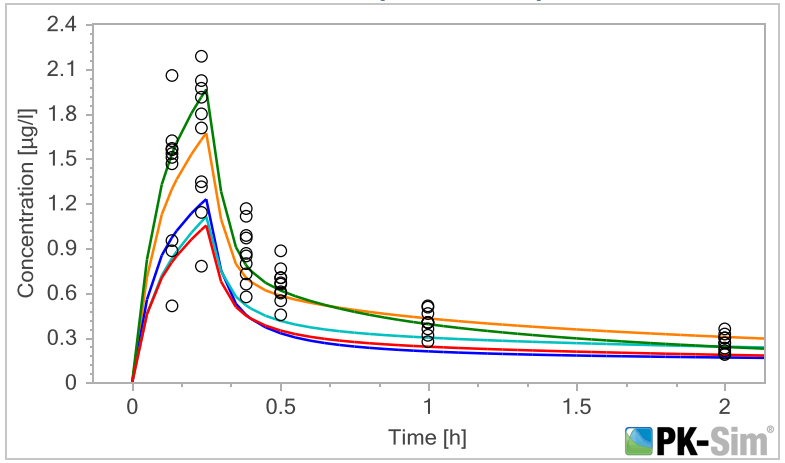
Establishment of a PBPK model

Visual assessment of the consistency between data and structural model/error model

Concentration-time profiles (log scale)



Concentration-time profiles (linear, zoom in)



- Additional visual inspections can provide more insight in model performance (e.g. goodness-of-fit plots, residuals vs. time, …)
- Relevant PK parameters (e.g. AUC, C_{max}) should be calculated from the simulation and compared to the observed values
- Identifiability issues should be evaluated

→ Selection of a “final” PBPK model has to integrate all the factors above

Establishment of a PBPK model

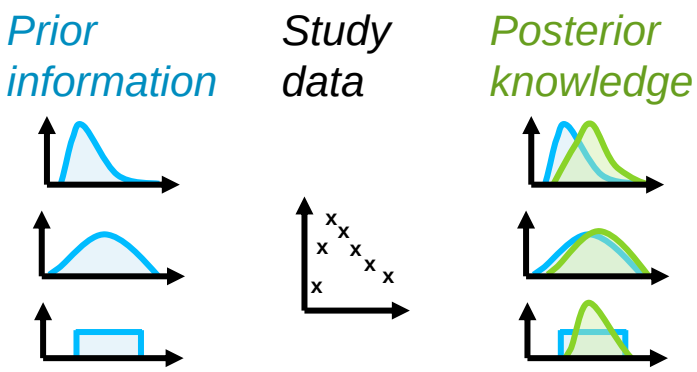
Bayesian approach to parameter identification

Bayesian statistics in a nutshell

- Combine prior knowledge with experimental data:

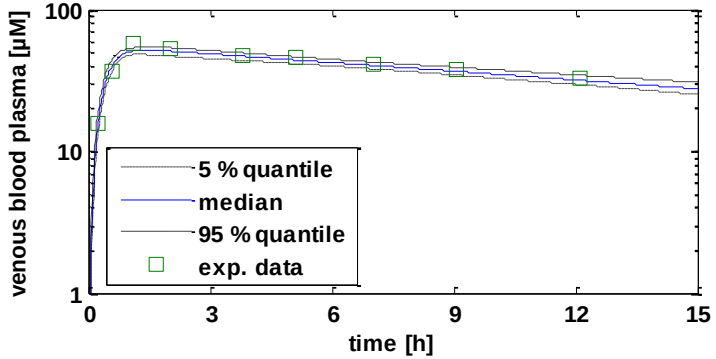
$$\underbrace{P(\theta|D)}_{\text{posterior}} \propto \overbrace{P(\theta)}^{\text{prior}} \cdot \overbrace{P(D|\theta)}^{\text{likelihood}}$$

- Parameters are random variables with a „true“ distribution

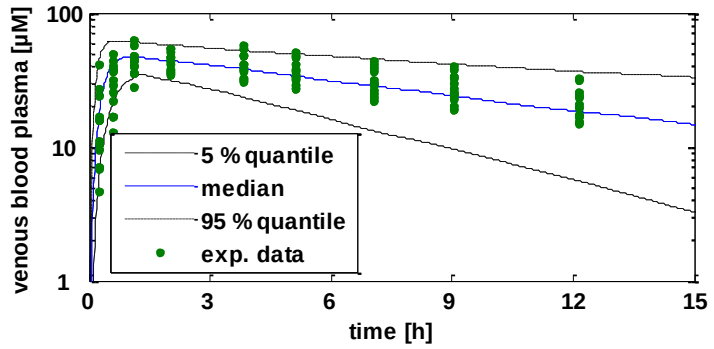


- Hierarchical models enable the separation of variability and uncertainty

Individual uncertainty



Population variability



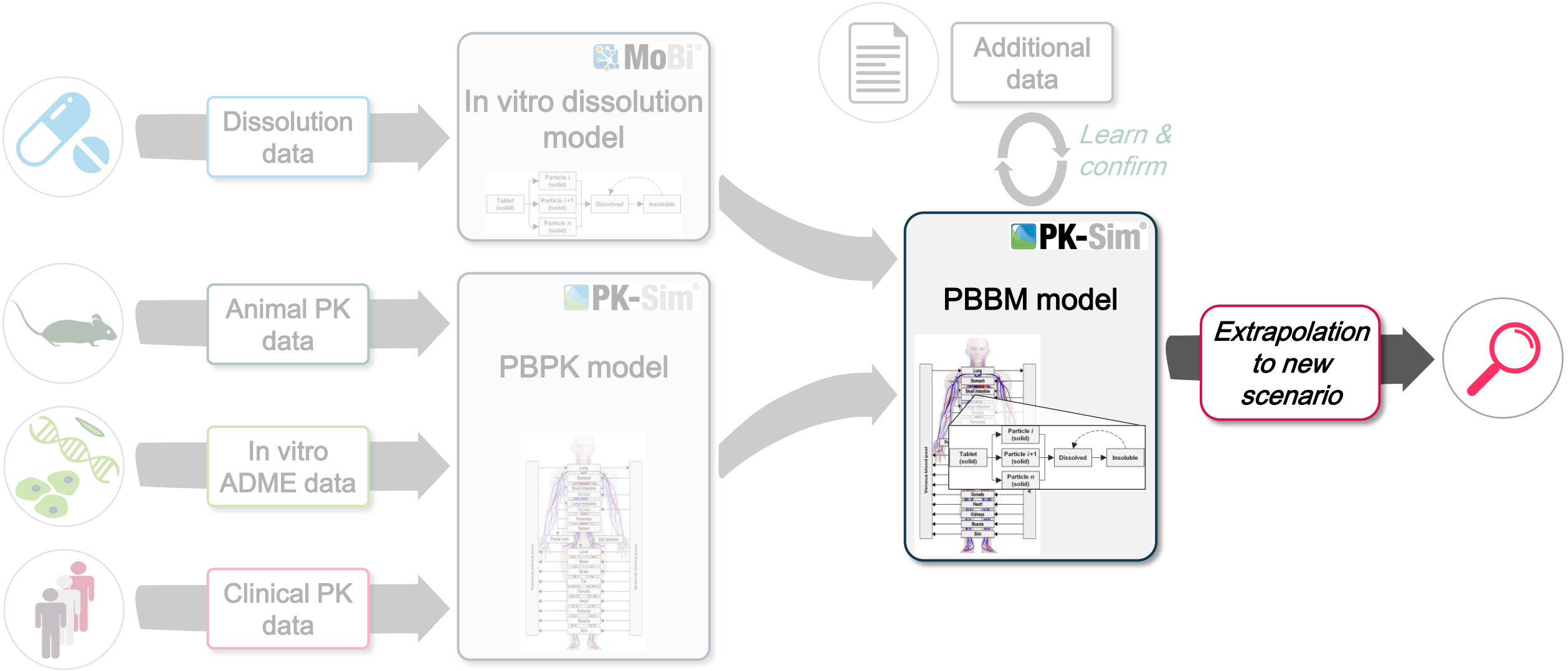
Establishment of a PBPK model

Recommendations for parameter optimization of PBPK models

- If possible, separate absorption from disposition procceses by consecutively developing a IV and oral PBPK model [1]
- Assess whether parameter estimates are physiologically plausible
- Visually inspect consistency between data and model (e.g. through concentration-time profiles, goodness-of-fit plots, residuals vs. time, …)
- Compare relevant observed PK parameters with simulated PK parameters
- Evaluate non-identifiability issues, imprecise parameter estimates and strong correlations between optimized parameters
- Take measures to avoid local minima, e.g.:
  - If the optimized parameter value is close to the upper or lower bound, modify the bound and repeat the optimization
  - Randomize start values of optimized parameters
  - Use a robust optimization algorithm (e.g. MCMC, simulated annealing)
- Preferably use Bayesian hierarchical model

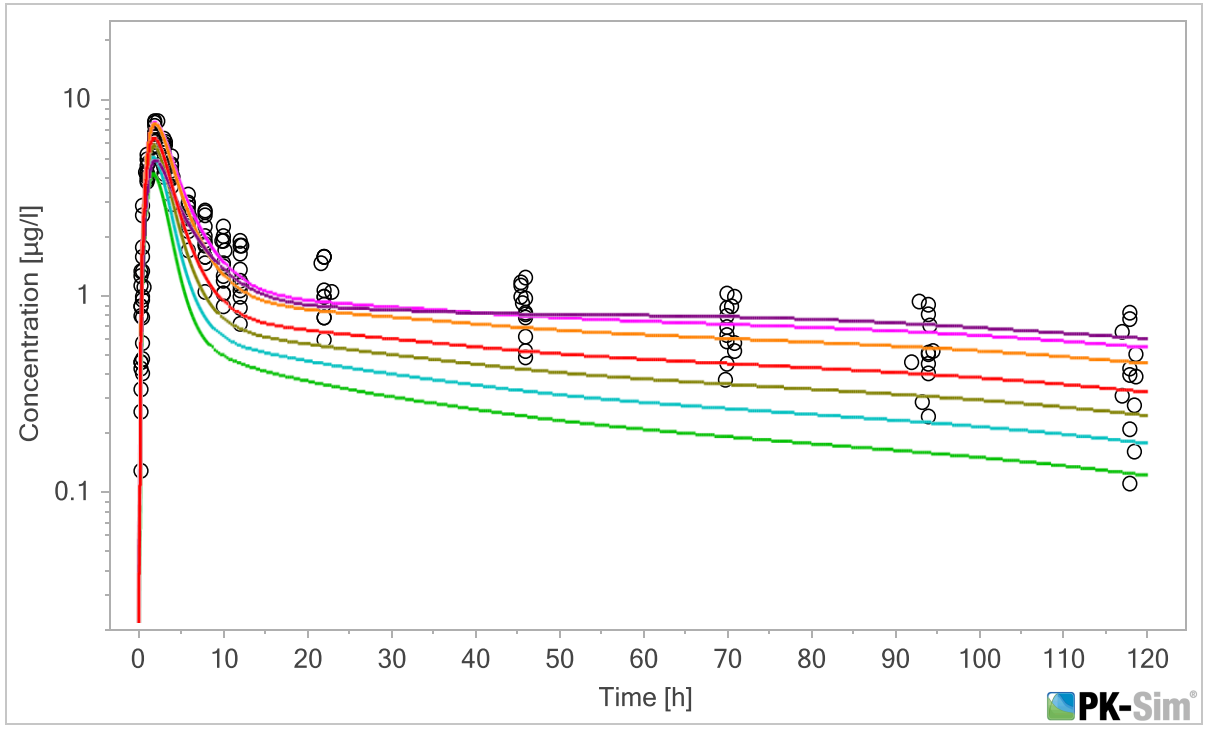
[1] Kuepfer, L. et al. 2016. doi: 10.1002/psp4.12134

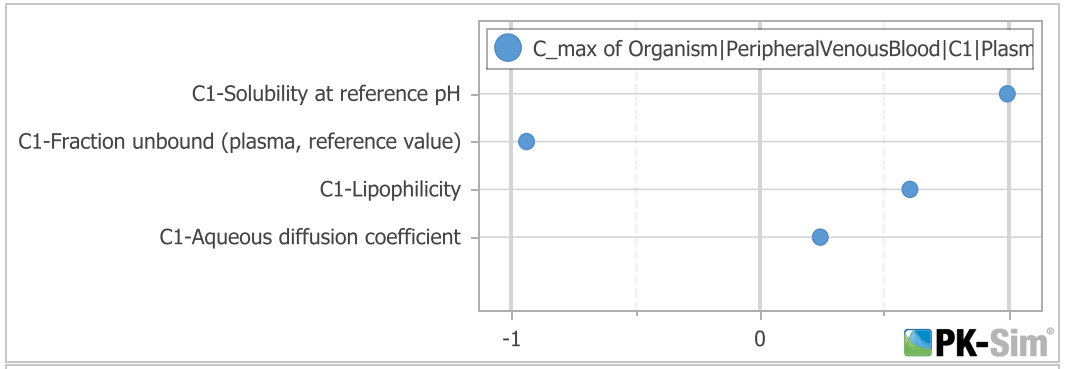
Workflow for PBBM model development

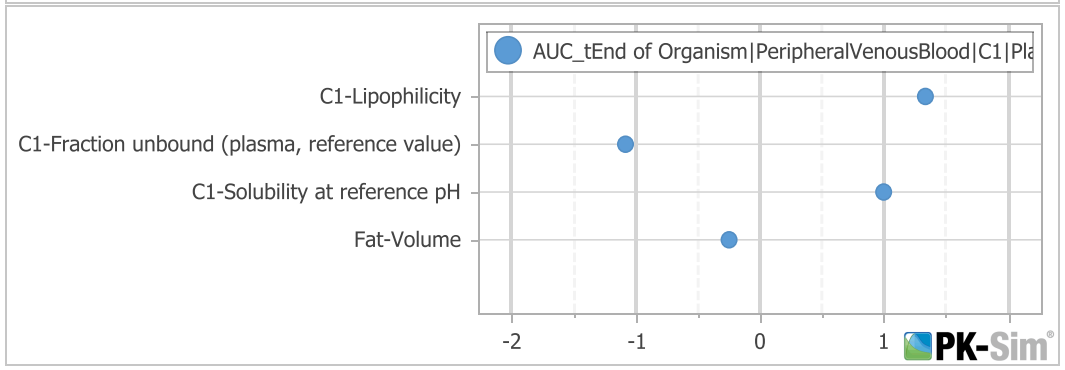


Coupling of dissolution and PBPK model

Propagation of parameter uncertainty to PBBM model output can be evaluated through sensitivity analyses







Coupling of dissolution and PBPK model

Recommendations for sensitivity analysis

- Conducted a sensitivity analysis using the “final” PBBM model application to assess how parameter uncertainty is propagated
- All optimized parameters should also be considered in the sensitivity analysis
- Parameter value ranges in the sensitivity analysis should reflect the uncertainty
- Give an interpretation of the sensitivity analysis results
- Conduct a worst case analysis

Conclusion

- Identifiability issues are critical because they can undermine mechanistic understanding and hinder translatability of the model to new scenarios
- Sensitivity analysis can be used to evaluate how parameter uncertainty is propagated to the PBBM model output
- Integration of Bayesian statistics into PBPK applications allows separate assessment of inter-individual variability and parameter uncertainty on simulated PK
- Despite multiple publications on Best Practices for PBPK modeling[1–5], no consensus has emerged yet
- Agreement and adoption of reference standards across stakeholders would be desirable
- The open science platform Open-Systems-Pharmacology (OSP) links different stakeholders and facilitates pre-competitive and transparent exchange, peer-review and qualification of models (http://www.open-systems-pharmacology.org/)

[1] Zhao, P. et al. 2012. doi: 10.1038/clpt.2012.68
[2] Shepard et al. 2015. doi: 10.1002/psp4.30
[3] Kuepfer, L. et al. 2016. doi: 10.1002/psp4.12134
[4] Marshall et al. 2016. doi: 10.1002/psp4.12049
[5] Shebley, M. et al. 2018. doi: 10.1002/cpt.1013

Thank you!

Bye-Bye